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David T. Hsieh and Bhagwan Moorjani

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Current thumbnail:
Incontinentia pigmenti is an X-linked dominant disorder with characteristic skin lesions and anomalies of teeth, hair, nails, eyes, and central nervous system. Cutaneous lesions are the most common identifiable abnormality and characterized in 4 stages. CNS abnormalities are the cause of most morbidity in this disorder. The NEMO gene is identified with this disorder. In this update, Drs. David Hsieh and Bhagwan Moorjani from Children's National Medical Center in Washington, DC highlight the reporting of reversible brain lesions by MRI, and the addition of the gothic palate in the spectrum of oral and dental anomalies in incontinentia pigmenti.

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~6. Historical note and nomenclature
Incontinentia pigmenti is an X-linked dominant disorder causing ectodermal dysplasia, with characteristic skin lesions and anomalies of teeth, hair, nails, eyes, and central nervous system (McKusick 1990). The disorder was first described by Garrod in 1906 but more clearly defined by Bardach in 1925, Block in 1926, Sulzberger in 1928, and Siemens in 1929 (Landy and Donnai 1993). The multiphasic and multisystemic nature of the disorder was first

recognized by Haber in 1952, at which time the eponym Bloch-Sulzberger syndrome was proposed. In 1961 Lenz first proposed X-linked dominant inheritance (Lenz 1961).
The term "incontinentia pigmenti" is a description of the characteristic leakage or "incontinence" of melanin, which appears outside melanocytes in the superficial dermis and basal layer of epidermis.

~7. Clinical manifestations

Cutaneous manifestations, which occur in 96% of familial cases of incontinentia pigmenti, are diagnostic; however, their absence does not exclude the diagnosis. Four overlapping and variable stages have been defined: vesicular, verrucous, hyperpigmented, and atrophic (Berlin 2002). Stage 1 is characterized by erythema and blisters at or shortly after birth. Vesiculo-bullous lesions or pustules appear in a linear pattern along the extremities |{Picture:incdg2.bmp}{caption:Skin in incontinentia pigmenti (2)}{label:Vesiculo-bullous lesions along the arm of an infant with incontinentia pigmenti. (Contributed by Dr. David Griesemer.)}| or circumferentially around the trunk.|{Picture:incdg1.bmp}{caption:Skin in incontinentia pigmenti (1)}{label:Vesiculo-bullous lesions on trunk of an infant with incontinentia pigmenti. (Contributed by Dr. David Griesemer.)}| Although several phases of blister formation may occur in different areas, most resolve by age 4 months. Eruptions may recur with febrile illnesses. Stage 2, which can be identified in two thirds of patients (Kegel 1987), is characterized by hyperpigmented, hyperkeratotic papules occurring in the same distribution as earlier blisters. Linear verruciform lesions appear on the hands, feet, and scalp, but they may be subtle and easily overlooked. Although most lesions resolve by age 6 months, they may recur throughout childhood (O'Brien and Feingold 1985). Stage 3 is characterized by the hallmark gray-brown, hyperpigmented macules of incontinentia pigmenti, which occur in 98% of patients (Carney 1976). These occur in streaks or whorls along Blaschko pigmentary lines, predominantly over the trunk in a distribution unrelated to that of earlier vesicles.|{Picture:incdg3.bmp}{caption:Hyperpigmented macules of incontinentia pigmenti}{label:Gray-brown macules occur in 98% of patients with incontinentia pigmenti. (Contributed by Dr. David Griesemer.)}| Macules become darker over weeks or months, but fade during early adolescence. As many as 40% of incontinentia pigmenti patients are born with verruciform or hyperpigmented lesions of Stage 2 and 3. Stage 4, which can be identified in 14% to 28% of incontinentia pigmenti patients, is characterized by pale streaks, which are most prominent over the calves. These appear lighter in color because of absent hair follicles and reduced vascularity (Moss and Ince 1987).

Systemic manifestations of incontinentia pigmenti are common. However, because it is difficult to recognize mildly-affected incontinentia pigmenti patients, true prevalences may be significantly higher than reported. Dental abnormalities occur in 60% of patients; these may include delayed, absent, or abnormal formation of teeth; teeth are typically peg-shaped or cone-shaped, but have normal enamel (Gorlin and Anderson 1960; Gordon and Gordon 1970; Vogt and Matheson 1991). In addition, the presence of a gothic (high arched) palate has been reported in one series (Minic 2006). |{Picture:incdg4.bmp}{caption:Dental abnormalities of incontinentia pigmenti}{label:Abnormally shaped teeth in a patient with incontinentia pigmenti. (Contributed by Dr. David Griesemer.)}| Minor abnormalities of hair and nails are also seen. Almost 50% of patients with incontinentia pigmenti have alopecia and scarring or coarse, wiry hair near the vertex (Carney 1976; Wiklund 1980). Whorled scalp lesions correspond to Blaschko lines of the scalp and may be associated with functional X chromosomal mosaicism (Chan et al 2003). About 40% of patients have nail dystrophy, typically mild but ranging from ridging or pitting to nail disruption or onychogryposis. Painful subungual, hyperkeratotic tumors and underlying deformities of the phalanges are occasionally seen (Hartman 1966; Simmons et al 1986). Supernumerary nipples and nipple or breast hypoplasia are also seen (Landy and Donnai 1993).

Significant neurologic problems occur in 10% to 30% of children with incontinentia pigmenti (Carney 1976; Landy and Donnai 1993), although the spectrum of neurologic abnormalities has not been carefully studied (Shuper et al 1990). Seizure disorders, including infantile spasms, occur in 13% of patients, although satisfactory control is often achieved. Severe mental retardation is seen in 15% of sporadic cases but in only 3% of familial cases (Landy and Donnai 1993). It has been reported that neonatal seizures indicates poor prognosis for normal development (O'Brien 1985), but Bryant and Rutledge (2007) recently reported of a patient with neonatal seizures, and also significant white matter disease by MRI with normal neurologic development. Spasticity occurs in 11% and delayed motor development in 7% (Carney 1976). Neuropathologic findings associated with seizures include polymicrogyria, neuronal heterotopia, and neuronal loss with microcephaly. In addition, ischemic and hemorrhagic cerebral vascular accidents are a recognized complication, though the etiologic pathophysiology is still debated. Other CNS problems include, dysgenesis of the corpus callosum, hydrocephalus, and ataxia (Hauw et al 1977; Tanaka et al 1990; Mangano and Barbagallo 1993; Hennel et al 2003). There has been a report of cortical necrosis and subcortical white matter involvement in a neonate presenting with acute encephalopathy, which was initially misdiagnosed as a viral encephalitis (Wolf et al 2005). Reports have also been made of reversible CNS white matter lesions (Yoshikawa 2000; Lou et al 2007), raising the question of whether CNS involvement occurs more often than previously reported.

Ocular abnormalities have been documented in 33% to 70% of children with incontinentia pigmenti (Rahi and Hungerford 1990; Landy and Donnai 1993; Holmstrom and Thoren 2000). These abnormalities include cataracts, keratitis, strabismus, nystagmus, uveitis, retinal pigment epithelial abnormalities, foveal hypoplasia, vitreous hemorrhage, and optic atrophy (Francois 1984; Lee et al 1995; Ferreira et al 1997). The most common problem is retinal ischemia, which produces extensive vascular remodeling, nonperfusion of retinal capillaries, and neovascular proliferation with subsequent hemorrhage and fibrosis (Heathcote et al 1991). This process is typically self-limited but may progress to clinically significant scarring or retinal detachment (Wald et al 1993). Serious visual impairment has been reported in up to 43% of patients with incontinentia pigmenti (Holmstrom and Thoren 2000).

Other less common anomalies have been reported in the literature as case reports. One report included limb truncation and primary pulmonary hypertension of one patient (Hayes et al 2005). Also reported in the literature is immune dysfunction with lower IgG IgG2 levels in a neonate (Pauly et al 2005).

~7a. Clinical vignette

A 50-day-old girl presented to the ER with 2 days of intermittent facial and body twitching. Her mother described the episodes of twitching as lasting 2 to 3 seconds, occurring primarily with crying and solely involving the right side of her face and right upper and lower extremities. There was no eye deviation, cyanosis, pallor, or apnea associated with the twitching. There was no recent fever or indications of illness. She had good oral intake and good urine output. Birth history was unremarkable. Family history was significant for mother with rash during childhood that gradually resolved by adulthood and maternal history of two prior spontaneous abortions. In the ER, patient was loaded with phenobarbital. Physical exam was significant for a hyperpigmented macular rash with surrounding macular erythema, primarily in the back, arms, and legs in a linear pattern. No vesicles or bullae were noted. Head CT showed nonspecific mild patchy edema of the L cerebral hemisphere. An MRI showed multifocal areas of abnormal restrictive effusions involving the L cerebral hemisphere and corpus callosum consistent with ischemic changes. MRA showed no aneurysms and no stenosis. Ophthalmologic exam was normal. PT/PTT were normal and no further hypercoagulable workup was pursued. EEG showed paucity of higher amplitude slow activity expected during the quiet sleep state. No

seizures were observed during her hospitalization and the patient was discharged with the diagnosis of incontinentia pigmenti.

~8. Etiology

Incontinentia pigmenti is inherited as an X-linked dominant disorder, which is lethal to boys in the prenatal period (Wettke-Schafer and Kanter 1983). This pattern of inheritance explains the dramatically high female to male ratio, female to female transmission, and the increased incidence of spontaneous abortions in families of children with incontinentia pigmenti (Wiklund and Weston 1980; O'Brien and Feingold 1985; Sefiani et al 1991). Approximately half of incontinentia pigmenti children have a family history of the disorder (Carney 1976); the remainder have sporadic mutations. Rarely, incontinentia pigmenti occurs in boys with Klinefelter syndrome (47,XXY) (Ormerod et al 1987; Prendiville et al 1989; Garcia-Dorado et al 1990). A few additional boys are born with incontinentia pigmenti, presumably on the basis of mosaicism, in which cells contain a normal and an abnormal X chromosome (Gorski and Burright 1993). Father to daughter transmission is exceedingly rare (Emery et al 1993).

~9. Pathogenesis and pathophysiology

Originally, 2 distinct gene loci for incontinentia pigmenti were identified on the X chromosome. Sporadic, nonfamilial incontinentia pigmenti has been characterized by autosomal translocations with X-chromosomal breakpoints within region Xp11 (Bernstein et al 1979; Hodgson et al 1985; Kajii et al 1985; Gorski et al 1991; Bitoun et al 1992). More recent data, however, suggest that patients with this translocation do not represent true cases of incontinentia pigmenti (Berlin et al 2002). The more accepted gene for familial incontinentia pigmenti has been mapped to Xq28 (Sefiani et al 1989; Sefiani et al 1991). It has been suggested that in X-linked dominant disorders, cell selection exists against cells expressing the defective allele on their active X chromosome. Non-random (skewed) X inactivation has been documented in only 35% of patients with incontinentia pigmenti (Harris et al 1992); however, it is present in the vast majority of individuals with Xq28-linked incontinentia pigmenti (Parrish et al 1996).

Recently, the gene for NEMO (NF-kappaB essential modulator) and IKK gamma (IkappaB kinase-gamma) has been mapped to 200 kilobases proximal to the factor VIII gene in Xq28. This gene is responsible for activating the transcription factor NF-kappaB, which is an important mediator in immune, inflammatory, and apoptotic pathways. Most incontinentia pigmenti patients have mutations of the NEMO gene. Ninety percent of cases were attributed to an identical genomic deletion (exons 4 to 10), resulting in genomic rearrangements at the NEMO locus (The International Incontinentia Pigmenti Consortium 2000; Smahi et al 2000; Aradhya et al 2001). Mutations of NEMO, which do not abolish NF-kappaB activity totally, permit male survival, causing an allelic variant of incontinentia pigmenti called hypohidrotic ectodermal dysplasia and immunodeficiency (HED-ID) (Martinez-Pomar et al 2005). It has been suggested that the apoptosis function associated with NF-kappaB accounts for much of the incontinentia pigmenti phenotype, including the retinal and central nervous system manifestations. Failure of the cells to resist apoptosis results in early cell death. Limb truncation likely related to the defect in NF-kappa B gene, which is responsible for formation of the apical ectodermal ridge at the tip of limb buds (Hayes et al 2005). Cytokines, growth factor, and modulators also interact with NF-kappa B and may explain the primary pulmonary hypertension documented in the literature (Hayes et al 2005). The modulation of immune function by NF-kappaB is likely related to the immune dysfunction reported in the literature (Pauly 2005).

Special interest has also been paid to eotaxin, an eosinophil-selective chemokine that has been isolated from the blister fluid of incontinentia pigmenti lesions. The promoter for eotaxin has an NF-kappaB binding site, and immunohistochemical staining of skin lesions from incontinentia pigmenti patients demonstrated strong expression of eotaxin throughout most of

the epidermal layers (Berlin et al 2002). Additionally, the X-inactivation status in female individuals contributes to the wide variety of phenotypes associated with this single common deletion (Aradhya et al 2001). Others have postulated that clinical findings result from an autoimmune attack on ectodermal cells, which express a surface antigen controlled by the mutant X chromosome gene (Person 1985).

MR imaging suggests the possibility of prenatal ischemic injury as a mechanism for occasional incontinentia pigmenti-related structural changes in the CNS (Mangano and Barbagallo 1993). Progressive microvascular changes may be a common pathogenesis of retinal and some CNS abnormalities (Lee et al 1995). MRI may demonstrate multiple scattered foci of restricted diffusion and decreased T2 signal within the periventricular white matter consistent with microvascular hemorrhagic infarcts. These abnormalities may progress to hemorrhagic necrosis. MRA may reveal decreased branching and poor filling of the distal middle and posterior cerebral arteries (Hennel et al 2003). These abnormalities have been postulated to relate to cerebral or cerebrovascular anomalies similar to those in the retina (Fiorillo et al 2003). Vascular abnormalities and occlusion of the retinal vessels are well described in the literature. It is possible that the retinal and cerebral vasculature share the same vulnerability due to inflammation or a hypersensitivity reaction to an abnormal protein expressed from a mutant gene (Lee et al 1995). Additionally, a microangiopathic process in the lungs may result in primary pulmonary hypertension (Hayes et al 2005).

~10. Epidemiology

Approximately 1 in 50,000 newborns are affected (Aradhya et al 2001). Skin involvement is the most common sign and 86% have stage I or II lesions, 80% were found to have stage III lesions, and 92% had stage IV lesions. Neurologic involvement, notably moderate to severe intellectual deficit was 8%. 37% were found to have eye abnormalities, the most common being strabismus. 95% had dental abnormalities. The NEMO gene deletion has been found in 80% to 90% of newborns (Phan et al 2005).

~11. Prevention

No information was provided by the author.

~12. Differential diagnosis

Early cutaneous findings must be distinguished from vesicular or bullous lesions common at birth. Noninfectious causes include erythema toxicum neonatorum, epidermolysis bullosa, dermatitis herpetiformis, drug eruptions, erythema multiforme, and neonatal lupus (Nelson-Adesokan and Mallory 1992), whereas common infectious causes include bullous impetigo, herpes simplex, and varicella zoster. Disorders that exhibit linear cutaneous lesions lines must also be distinguished from incontinentia pigmenti. One of these is hypomelanosis of Ito, which is also called incontinentia pigmenti *achromians*. Clinical findings in hypomelanosis of Ito include mental retardation, seizures, skeletal dysplasia, and depigmentation following Blaschko lines, resulting from a decrease in melanin in the basal layer of epidermis. Another disorder is X-linked chondrodysplasia punctata, which is distinct because of its linear scarring with follicular pitting, skeletal dysplasia, and congenital cataracts. Finally, disorders of hyperpigmentation must be differentiated from incontinentia pigmenti. Examples include multisystem disorders with café-au-lait or brown spots, such as neurofibromatosis, Silver-Russell syndrome, tuberous sclerosis, and Albright syndrome (Fulk 1984; Zillikens et al 1991). The differential diagnosis of vesicular and linear lesions is broad, and a dermatologist should be consulted if diagnostic questions remain. However, the presence of primary skeletal abnormalities or severe neurologic impairment in early stages makes the diagnosis of incontinentia pigmenti less likely.

~13. Diagnostic workup

No information was provided by the author.

~14. Prognosis and complications

Patients with incontinentia pigmenti appear to be at increased risk of CNS infection (Siemes et al 1978; Diamantopoulos et al 1985; Barson and Reiner 1986), which may be related to defective neutrophil chemotaxis (Menni et al 1990). Although infrequent, other reported CNS complications include hemorrhagic or necrotic encephalopathy (McPherson and Auth 1963; Siemes et al 1978; Avrahami et al 1985; Shuper et al 1990), recurrent encephalomyelitis and optic neuritis with depletion of T8 suppressor cells and increase in the T4:T8 ratio (Brunquell 1987), and anterior horn cell degeneration (Larsen et al 1987). Risk of malignancy also appears to be increased in incontinentia pigmenti children under age 3 years (Roberts et al 1988). Late reactivation is possible, but rare, and most often associated with viral or bacterial infection (Patrizi et al 2004). At an older age, the following may occur: slowing down of motor function, muscular weakness, mental retardation, and convulsions (Buinauskiene et al 2005).

~15. Management

Clinical diagnosis on the basis of the hallmark hyperpigmented lesions in whorling or linear patterns is often possible. However, during the vesicular or verruciform stages, skin biopsy and direct immunofluorescence is helpful. In Stage 1, histologic studies show intraepidermal infiltration of eosinophils. In Stage 2, the epidermis is acanthotic and hyperkeratotic with papillomatosis (Lever and Schaumburg-Lever 1990). In Stage 3, melanin is seen in the papillary dermis, and vacuoles are seen in the basal cell layer. Electron microscopy shows gaps in the basement membrane where fetal nerves enter the epidermis (Worrett et al 1988). In Stage 4, there is epidermal atrophy with reduced melanocytes and absence of adnexal structures (Lever and Schaumburg-Lever 1990; Nazzaro et al 1990; Zillikens et al 1991). Colloid bodies similar to Civatte bodies of lichen planus and lupus erythematosus have also been identified in the upper dermis by means of electron microscopy (Berlin et al 2002). Histologic examination is especially important with atypical symptoms that may suggest chromosomal mosaicism. Biopsy may also be helpful with older children or adults in whom cutaneous findings may be minimal. Bedside diagnosis in neonates may be facilitated by unroofing a vesicle and observing eosinophils in the fluid under light microscopy. A Tzanck preparation, bacterial and viral cultures, and complete blood count may further narrow the differential diagnosis (Nelson-Adesokan and Mallory 1992), as significant leukocytosis with eosinophilia is seen during the vesicular stage of incontinentia pigmenti (Carney 1976). The presence of cone-shaped teeth, nail dysplasia, patchy alopecia, or retinal dysplasia may further suggest the need for biopsy in children who do not have typical cutaneous involvement.

Increased use of MR angiography and spectroscopy has permitted the identification of acute or chronic cerebrovascular disease not previously recognized. MR findings reported in patients with incontinentia pigmenti include small vessel occlusions, hypoplasia of the corpus callosum, enlargement of the lateral ventricles, and periventricular white matter disease (Lee et al 1995; Aydingoz and Midia 1998). Because neuroimaging have not been routinely ordered in incontinentia pigmenti, the frequency of CVA may be underestimated (Fiorillo et al 2003).

Periodic neurologic and psychoeducational evaluations of patients with incontinentia pigmenti should be performed to identify motor, developmental, or cognitive problems. MR imaging is recommended to document dysplastic or ischemic brain malformations. Standard strategies for treatment of infantile spasms or other seizures are required in some patients; however, subclinical epileptiform discharges may be seen in others (Bitoun et al 1992). Because of ocular anomalies associated with incontinentia pigmenti, serial retinal examination is recommended during the first year of life. Fluorescein angiography may be recommended to further evaluate occult areas of neovascularization and leakage that may progress to retinal

detachment and decreased vision (Shaikh et al 2004). Retinal neovascularization may be treated with xenon photocoagulation (Nishimura et al 1980) or cryotherapy (Rahi and Hungerford 1990). Retinal detachment may require vitreous surgery (Wald et al 1993). The prognosis for normal vision is excellent if incontinentia pigmenti children do not have retinal abnormalities during the first year of life (Rahi and Hungerford 1990). Finally, regular dental evaluations are important to plan for orthodontic treatment in selected patients.

Comprehensive genetic counseling is essential. It is important to obtain a family history, including history of spontaneous abortions, and to examine all women and girls in the family as potential gene carriers. Because girls with sporadic incontinentia pigmenti are often severely affected, chromosome analysis is indicated for patients with atypical or severe symptoms and all presumably affected boys (Gorski and Burright 1993). Genetic testing for the common NEMO gene mutation is now available. This testing is performed at Baylor College of Medicine DNA Diagnostic Laboratory (Houston, Texas; phone: 800-BCM-DNA4; Web site: |{WebSite:BCM Medical Genetics Laboratories}{WebURL:http://www.bcmgeneticlabs.org}|).

Support groups and additional educational information for patients and their families is available through the |{WebSite:Incontinentia Pigmenti International Foundation}{WebURL:http://imgen.bcm.tmc.edu/ipif/}| (30 East 72nd St, 16th Floor, New York, NY 10021; phone: 212-452-1231) and the Incontinentia Pigmenti Support Network (34929 Elm, Wayne, MI 48184; phone: 313-729-7912) (Berlin et al 2002).

~16. Pregnancy

A woman with incontinentia pigmenti has a 50% chance of contributing a normal X chromosome and a 50% chance of contributing an abnormal X chromosome to each child. The daughter or son receiving a normal X chromosome will be unaffected. The daughter receiving an abnormal X chromosome from the mother and a normal X chromosome from the father will have incontinentia pigmenti. The son receiving an abnormal X chromosome from the mother and a normal Y chromosome from the father, will also have incontinentia pigmenti but will likely die in utero. The frequency of spontaneous abortions in familial incontinentia pigmenti is 23%, corresponding to the 1 in 4 chance of a child receiving the incontinentia pigmenti-mutated X chromosome from the mother and a Y chromosome from the father (Wettke-Schafer and Kanter 1983).

~17. Anesthesia

No information was provided by the author.

~18. References cited

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**References especially recommended by the author or editor for general reading.

~19. Abbreviations
CNS:central nervous system
CT:computed tomography
MR:magnetic resonance

~20. ICD codes
ICD-9:
Incontinentia pigmenti: 757.33

ICD-10:
Incontinentia pigmenti: Q82.3

~20a. OMIM number
Incontinentia pigmenti: #308300

~21. Synonyms
Bloch-Sulzberger syndrome

~24. Major keyword descriptors
Blaschko lines
ectodermal dysplasia
hyperpigmentation
infantile spasms
neurocutaneous syndrome
phakomatosis
rash
retinal detachment
retinal neovascularization
seizures
spasticity
vesicles

X-chromosome
CVA

~25. Minor keyword descriptors
anterior horn cell
cerebral dysgenesis
dental abnormality
eosinophilia
Klinefelter syndrome
microcephaly
microphthalmos
mosaicism
nystagmus
optic nerve atrophy
strabismus

~26. Age of presentation
0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

~27. Age of typical presentation
0-01 month
01-23 months
02-05 years

~28. Population group(s) preferentially affected
none selectively affected

~30. Occupation group(s) preferentially affected
none selectively affected

~32. Sex
female>male, >2:1
female>male, >1:1

~33. Family history
family history typical

~34. Heredity
heredity typical
heredity may be a factor
X-linked dominant

~36. Permuted topic, synonyms, subtopics
Incontinentia pigmenti

pigmenti, Incontinentia
Sulzberger syndrome, Bloch-

~37. Related topics
Focal cortical dysplasia
Hypomelanosis of Ito
Neurocutaneous syndromes

~38. Differential diagnosis
vesicular lesions
bullous lesions
hypomelanosis of Ito
incontinentia pigmenti *achromians*
X-linked chondrodysplasia punctata
hyperpigmentation
neurofibromatosis
Silver-Russell syndrome
tuberous sclerosis
Albright syndrome
erythema toxicum neonatorum
epidermolysis bullosa
dermatis herpetiformis
drug eruptions
erythema multiforme
neonatal lupus
bullous impetigo
herpes simplex
varicella zoster
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